Factors That May Predict Fatigue in Women with Newly-Diagnosed Breast Cancer: Pain, Depression, Worry, Pain, Sleep Disturbances

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Background

Breast cancer is a serious disease. It can lead to significant life changes, and impact women and their loved ones in multiples ways. It is important to understand the physical and psychological symptoms in newly diagnosed breast cancer patients, and their effect on the three stages of survivorship. The acute stage of survivorship includes active treatment with surgery, chemotherapy, or radiation therapy, whereas the extended stage of survivorship defines the completion of active treatment, early remission, and beyond (Department of Health and Human Services [DHHS], 2004). Permanent survivorship is long-term survival without evidence of recurrence. The survivorship approach is so critical. Psychosocial care should be integrated into the routine care of all patients with cancer and be recognized as a new standard of care (Holland et al., 2013).

To improve treatment of physical and psychosocial symptoms, we must first identify prominent symptoms that may affect the breast cancer experience. In addition, we must identify when these symptoms occur, and how they present in order to improve care. The identification of persistent symptoms provides opportunities to target interventions for survivors and improve their outcomes (Lester et al., 2015). Overall, a better understanding of these bothersome symptoms can enlighten professionals caring for breast cancer survivors and illuminate supportive care pathways.

Conceptual Framework

Our study framework and analyses are based on the Lenz theory of unpleasant symptoms which illustrates the variety of factors that can contribute to overall patient performance. This theory is based on the premise that commonalities are found across different symptoms that may be experienced by clinical populations in a variety of situations (Lenz, Pugh, 2008). This theory

enabled us to visualize the possible physiologic, psychologic, and situational factors that may lead to the group of self-reported symptoms of pain, worry, depression, and sleep disturbances, and to observe their effect on patient performance as related to fatigue (Figure 1).

Pain

In a study of women with newly-diagnosed breast cancer (N=100), pain was self-reported 36% of the time among survivors sampled during treatment, at its end, and three and six months post treatment (Lester et al., 2015). These findings are consistent with Denieffe, Cowman, Gooney (2014) who analyzed symptoms that breast cancer patients were experiencing prior to surgical interventions. Results identified pain as a prevalent symptom (Denieffe et al., 2014).

Other studies confirm that pain is a critical symptom that must be examined. In a case study performed by Westerlin (2014), results showed that pain was seen as a common factor throughout the disease process of cancer. Furthermore, Westerlin's (2014) work showed that individualized pain management is extremely beneficial and can improve the quality of life of survivors. Overall, research findings demonstrate that pain is a significant symptom in the breast cancer experience and must be addressed.

Sleep Disturbances

Sleep disturbances are another troublesome symptom experienced by women with breast cancer. Its occurrence was self-reported 52% of the time in newly-diagnosed breast cancer survivors (Lester et al., 2015). Sleep disturbance is a very concerning side effect as alterations in sleep can negatively influence the risk of infectious disease, major medical illnesses including cardiovascular disease and cancer, and the incidence of depression (Irwin, 2015). It is important to examine sleep as it plays a critical role in the overall well-being of newly diagnosed breast cancer patients (Irwin, 2015).

In a study of breast cancer survivors (N=861) at a single institution, multiple variables were found to affect factors of sleep (Klyushnenkova, Sorkin, Gallicchio, 2015). Independent risk factors for excessive daytime sleepiness included younger age, acute pain, and lower level of education. Independent factors of 'short' sleepers (e.g. less than six hours per night) included African American race, presence of acute pain, and lower level of education (Klyushnenkova et al., 2015). Body mass index was not a contributing factor to sleep disturbances, a factor postulated by the authors. In a separate study of young breast cancer survivors (N=163), sleep disturbance was identified as a mediator (64%) between the significant association ($P<0.001$) of increased vasomotor symptoms and depression (Accortt, Bower, Stanton, Ganz, 2015). The authors proposed that interventions to improve sleep deprivation may decrease the occurrence of depression (Accortt, et al., 2015), yet another prevalent symptoms in breast cancer survivors (Lester et al., 2015)

Fatigue

Fatigue is another common symptom reported by cancer patients. Fatigue was self-reported at a rate of 56% in the study of newly-diagnosed and treated breast cancer survivors (Lester et al., 2015). Researchers further supported that fatigue was a burden in the cancer survivor experience (Mackereth et al., 2015;. In a focus group of women who had experienced breast cancer, fatigue was listed as a significant current symptom (Mackereth et al., 2015). Furthermore, these women described fatigue as have effects on multiple aspects of their lives, including relationships, sexuality, social life, home life, and return to work (Mackereth et al., 2015).

As noted above, fatigue can be a difficult symptom for breast cancer survivors during and after treatment, and even years after the end of active treatment (Mortimer et al, 2010; Stone et

al., 2000). Breast cancer patients continue to experience fatigue symptoms for months or even years after successful treatment. Stone and colleagues (2000) observed that 75% of patients with solid tumors experienced significant levels of fatigue as compared to a healthy matched control population. Fatigue was listed as a primary source of bothersome symptoms in early breast cancer survivors (Lester et al, 2015).

Worry

Worry was also considered a serious symptom among our breast cancer survivors with a self-reported rate of 55% (Lester et al., 2015). The timing of worry may be significant in that worry increases along the breast cancer trajectory, with a significant increase ($P<0.05$) after the end of active treatment (Lester et al., 2015). Worry is seen as an emotional problem that can likewise cause increased distress (Tavernier, 2014). It is important to further explore the cardinal symptom of increased worry and how professionals can help women better understand their disease and expected outcomes (Janz et al., 2014).

In a retrospective, population-based statistical analysis of The National Health Interview Survey (NHIS) data (N=2,668, 697 breast cancer survivors), worry about recurrence was a prevalent symptom that was correlated with several variables: age ($P = 0.03$), history of radiation therapy ($P = 0.04$), perceived risk of recurrence ($P < 0.01$), decreased overall quality of life ($P < 0.01$), and lower self-reported physical ($P < 0.01$) and mental ($P < 0.01$) health, as well as decreased satisfaction with social activities and relationships ($P < 0.01$; Tewari, Chagpar, 2014). Women who always worried about breast cancer recurrence had a lower quality of life (OR, 0.06; 95% confidence interval, 0.01 to 0.45; Tewari, Chagpar, 2014). Therefore, screening for worry is an important intervention to establish the knowledge base of each survivor, and their

particular triggers. It remains unknown how symptoms of pain, sleep deprivation, depression and worry may affect the overall syndrome of fatigue.

Purpose

The purpose of this secondary analysis was to examine the level and source of bothersome symptoms (worry, depression, pain, sleep disturbances) over time (at diagnosis, during treatment, at treatment end, and three months later) and the relationships between these variables and their effect on fatigue.

Methods

Research Design

A longitudinal design with repeated measures was used to examine relationships between self-reported symptoms of pain, sleep disturbances, worry, and depression in breast cancer survivors and their effect on performance as related to fatigue.

Sample

Women were accrued from November 2013 through March 2014 from surgical and medical oncology clinics in a freestanding comprehensive breast center at a large, university-based, National Cancer Institute–designated comprehensive cancer center. The Cancer Institutional Review Board at the Ohio State University in Columbus, Ohio approved the study. The study sample met inclusion criteria of females with a recent diagnosis of breast cancer (0-8 weeks), Stage 0, I, II, or III breast cancer, age 18 or older, able to provide consent, willing to complete questionnaires every 3-6 months for up to four years after the end of active treatment, able to read, write, and communicate in English, and no significant mental health conditions impairing cognition (e.g. schizophrenia, mental retardation, dementia).

The study sample included 150 women with newly diagnosed breast cancer that self-reported distress and associated symptoms at noted time points from diagnosis, active treatment, and possibly three months post-treatment. Women completed their self-reported questionnaires at specific time points as designated in the study: at diagnosis, during active treatment, at treatment end, and 3 months later. The time period designated as 'diagnosis' included the initial diagnosis and perhaps surgery that completed their pathologic diagnosis. Other women may have delayed surgery and started with neoadjuvant chemotherapy (e.g. before surgery), so their second time point may be during chemotherapy. Therefore, the time points were dependent on each individual treatment trajectory as some women remained in active treatment (surgery, chemotherapy, radiation therapy) for over a year, with transposition of surgery and chemotherapy. Outcome measures included the self-reported occurrence, location, and intensity of pain, intensity of fatigue and interference in daily activities, depression, worry, and sleep disturbances.

Measures

Distress thermometer problem list: Self-reported measures were obtained using the National Comprehensive Cancer Network (NCCN) Distress Thermometer (NCCN, 2014), a brief, self-report instrument that provided screening data about patient-reported distress surrounding their cancer diagnosis and its impact on their psychological status. The 38-item problem list utilizes yes/no answer options. The problem list represents five subscales: emotional sources (6 items) including depression and worry, physical sources (21 items) including fatigue, pain, and sleep disturbances, practical sources (6 items), spiritual sources (1 item), and family sources (4 items). Items are totaled, with possible subscale scores or a total item score ranging from 0 to 38, with identification of varying levels of intensity of distress for individual items.

Two author-derived free response items were included to elicit individual disease-related issues: "What are your top three causes of distress" and "What are your three most distressing symptoms".

Demographic and caregiver information: The demographic form was comprised of self-report items related to information about changes in residence, responsibilities, specific caregiver and support system. Items included county of residence/state, zip code, level of education, marital status, dependents in household under age 18, age of dependents, dependents in household over 18, age of dependents, other dependent responsibilities such as adult children/grandchildren/elderly parents, household income before cancer diagnosis, current household income, employment status, previous/current occupation, health insurance status/type of insurance, primary support person(s) related to cancer treatment- relationship (age/gender/county/state), primary caregiver related to cancer treatment- relationship (age/gender/county/state), religious preference, and rating of health status.

Brief pain inventory: The Brief Pain Inventory is a self-report questionnaire with 14 items that are designed to assess the occurrence, location, and intensity of pain. The five-item Likert-type scale represents a sensory dimension that enables measurement of pain intensity and potential increases or decreased related to interventions. The seven-item reactive dimension is used to measure the interference of pain in daily life. Each of the reactive items are scaled from 0-10; 0 = 'no pain/interference at all', and 10 = 'pain as bad as you can imagine / complete interference. The diagram enables the participant to mark directly where the pain is experienced (Tan, Jensen, Thornby, and Shanti, 2004).

The Brief Pain Inventory has been validated in numerous studies and multiple languages. In a study of patients with chronic intractable back pain (N = 440) internal consistency was

established with Cronbach alpha coefficients: 0.85 for intensity items and 0.88 for interference items (Tan et al., 2004). Factor analysis supported the two factor structure of intensity ($r = 0.57$) and interference ($r = 0.40$, $t = 5.71$, $P < 0.01$); correlation with interference (0.80) supported that the scales assessed related, although distinct dimensions (Tan et al., 2004). In addition, the brief pain inventory was sensitive to the measurement of improved pain with treatment, which indicates the brief pain inventory can accurately survey pain over time (Tan et al., 2004).

A second study that used the Brief Pain Inventory to survey cancer patients (N=258) with painful bone metastasis demonstrated internal consistency of subscales of pain, activity interference, and affect interference with Cronbach's alpha (0.81 - 0.89; Wu, Beaton, Smith, and Hagen, 2010) Confirmatory factor analysis demonstrated significance for all factor loadings (t values 8.7 – 17.7); convergent validity was also supported for the respective factors (Wu et al., 2010). Composite reliability demonstrated internal consistency of the three-factor structure (0.76 – 1.0) with a minimal acceptable level of 0.70 (Wu et al., 2010). In a study of HIV/AIDS and cancer patients (N = 364), the brief pain inventory was studied to compare a one-factor model to a two- or three-factor model (e.g. intensity, activity interference, and affect interference).

Brief fatigue inventory: The Brief Fatigue Inventory was designed to measure the severity or intensity of fatigue, and the impact, or interference on daily functioning. The population intended is patients with fatigue related to cancer and cancer treatment. Reliability of the instrument was measured with Cronbach's alpha (0.82 – 0.97; MD Anderson Cancer Center [MDACC], 2012) A global fatigue score can be obtained by examining all completed items to obtain an average score (MDACC, 2012). The Brief Fatigue Inventory has been translated into a number of languages with psychometric testing. The Brief Fatigue Inventory was studied in head and neck cancer patients (N=52) as compared to controls (N=57) to measure the intensity and

frequency of fatigue (Aynehchi, Obourn, Sundaram, Bentsianov, and Rosenfeld, 2013). The one-week test-retest reliability scores were calculated with Cronbach's alpha ($r=0.80$, $P < 0.001$); internal consistency was also calculated with Cronbach's alpha ($\acute{\alpha} = -.938$; Aynehchi et al., 2013). Construct validity was compared with the Multidimensional Fatigue Symptom Inventory ($r = 0.814$, $P < 0.001$); discriminant validity compared the cancer patients and controls ($P = 0.027$) and was non-significant (Aynehchi et al., 2013).

Patient health questionnaire: The Patient Health Questionnaire (PHQ-9) is a self-report scale that assesses symptoms of major depressive disorders as defined by the DSM-IV. The domain is depressive symptoms and its accompanying functional impairment. The traditional cutoff score for the PHQ-9 is ≥ 10. The Panel's recommended cut score of ≥8 is based on a study of the diagnostic accuracy of the PHQ-9 with cancer outpatients. A meta-analysis also supported ≥8 cutoff score (Kroenke, Spitzer, Williams, 2001; Menea, Gilbody, McMillan, 2012).

Generalized anxiety disorder (GAD-7) scale: The Generalized Anxiety Disorder (GAD-7) Scale is a self-report scale assessing probably causes of generalized anxiety disorder. (GAD-7) is a seven-item scale intended to measure GAD symptomatology. Persons with GAD do not necessarily present with symptoms of anxiety, per se. The GAD symptoms, i.e. multiple excessive worries may present as 'concerns' or 'fears'. Whereas cancer worries may be common for many, GAD worry or fear may be disproportionate to actual cancer-related risk, e.g. excessive fear of recurrence, worry about multiple symptoms, or symptoms not associated with current disease or treatments. Importantly, an individual with GAD has worries about a range of other, non-cancer topics in areas of his/her life (Spitzer, Kroenke, Williams, 2006)

Data Analyses

Descriptive analyses: Demographic data (categorical and continuous data) were summarized using descriptive statistics such as frequencies and percentages across type of cancer (categorical data), and visit time (categorical data). With consideration to the specific parameter, central tendencies were reported; means and standard deviations were calculated as appropriate.

Primary analyses: Chi square was used to identify relationships between categorical variables and time periods; post hoc tests using Bonferonni were applied to determine significance to specified time periods. Analysis of variance (ANOVA) was used to identify relationships between continuous variables and time periods; post hoc tests using Tukey's were applied to determine significance to specified time periods. Multivariate analysis of variance (MANOVA) was used to examine relationships between specific symptoms, fatigue, and specific time periods. Linear stepwise regression was used to identify symptom predictors of fatigue in the first year of treatment. Each symptom (e.g. depression, worry, pain, and sleep disturbances) were measured to determine significant findings.

Results

Presence of Symptoms

The presence or absence of each self-reported symptom was examined for each time period using yes/no response options on respective measurement instruments. We found that the four most common time periods of participant self-reporting were at diagnosis, during treatment, during continued treatment, and end of treatment. Depending on the length of systemic treatment, women with breast cancer could be 'in treatment' for over 18 months. Therefore, the time points used for statistical considerations were adjusted to those listed above with elimination of the time period of 3 months after end of treatment. The relationship of time to the

presence of specific symptoms was examined and displayed by significant Chi-square findings (Table 1).

Pain: Participants self-reported the presence of pain (Table 1) at diagnosis (38%), during treatment (28%), during treatment (35%) and end of treatment (31%) correlating to the data collected during the three month time periods in year one of the breast cancer trajectory. There were no significant differences between time periods (P = 0.6) indicating that pain was a common and ongoing symptom for at least one-third of women throughout the first year of their breast cancer trajectory.

Sleep disturbances: Participants again self-reported the presence of sleep disturbances (Table 1) at various time points: at diagnosis (53%), during treatment (48%), during treatment (48%), and end of treatment (48%). There were no significant differences between time periods (p = 0.7), which indicate that sleep disturbances were present throughout the first year breast cancer trajectory, albeit present in nearly 50% over all women.

Worry: The self-reported presence of worry (Table 1) indicated a significant difference between time periods, with worry increasing along the breast cancer trajectory (P=0.004). The presence of worry at each time period included at diagnosis (3%), during treatment (17%), during treatment (17%), and at treatment end (24%).

Depression: Depression was most commonly reported using the response 'some of the time' on the PHQ-9. Few persons responded to the other answer options. Therefore, for ease of analyses the persons who indicated some of the time were evaluated (Table 1). At diagnosis, depression was present 'some of the time' (32%), during treatment (30%), during treatment (35%), and at end of treatment (38%). There was no significant difference of depression between

time periods (P=0.5). These findings indicate that depression was present 'some of the time' throughout the breast cancer trajectory by most of the breast cancer survivors.

Fatigue: Participants self-reported the presence of fatigue (Table 1) at diagnosis (56%), during treatment (58%), during treatment (49%), and end of treatment (34%) with significant differences across time periods ($p = 0.001$). These findings signify that the presence of fatigue decreased by 22% at the end of treatment.

Determinants of Fatigue

Relationships between fatigue and pain, sleep disturbances, worry, or depression were calculated for each time period (Table 2). For the symptoms of worry, a significant relationship with fatigue was noted during treatment ($p<0.00$) and end of treatment ($p=0.01$). The symptom of depression was significant with fatigue at all four time periods: at diagnosis ($p<0.00$), during two consecutive time periods of active treatment ($p<0.00$; $p=0.05$, respectively) and at end of treatment ($p<0.004$). Pain was also significant with fatigue at all four time periods ($p<0.00$, $p<0.001$, $p<0.00$ and $p<0.00$, respectively). Finally, sleep disturbances was also significant at all four time periods ($p<0.00$, $p=0.03$, $p<0.00$, and $p<0.00$, respectively). Overall, significant relationships were seen at all four time points between fatigue and depression, pain, and sleep disturbances. These finding indicate the ongoing presence of these symptoms, and their significant relationships with fatigue. Worry was significant during early treatment ($p<0.00$) and at its end ($p=0.01$), signifying a decrease after diagnosis albeit a significant increase at the end of treatment.

Predictive Variables for Fatigue

Finally, we performed linear stepwise regression to identify the potential relationship(s) between the predictability of each variable for fatigue during the first year of treatment (Table 3).

These analyses indicated that depression, pain, and sleep disturbances are individually and collectively significantly predictive of fatigue in the first year of treatment at all four times points ($P<0.00$). Sleep disturbances was the most significant predictive factor of fatigue. Depression, pain, and worry were predictive of fatigue in that order, respectively.

Discussion

Secondary analyses of significant bothersome symptoms that occurred in breast cancer survivors during the diagnostic, active, and end of treatment time periods of early survivorship and their potential significant relationships with fatigue were examined. Overall, we found that across the time periods of diagnosis, active treatment, and its end, women with breast cancer suffered from a number of significant and bothersome symptoms: pain, sleep disturbances, worry, depression, and fatigue. These findings were congruent with those of previous researchers as described earlier in this article. In addition, using fatigue as a dependent variable or constant, we found that pain, sleep disturbances, and depression were individually and collectively predictive of fatigue during diagnosis, active treatment, and its end, while worry was significant at diagnosis and end of treatment.

Fatigue is one of the most common symptoms reported by cancer survivors, including women with breast cancer (Lester, 2015). Our findings indicated significant relationships between specific symptoms and time periods in early survivorship and their predictive effect on fatigue. As expected, sleep disturbances was the most significant and persistent symptom that predicted fatigue, although the other symptoms were likewise independent predictors. The relationships between fatigue and worry, depression, pain and sleep disturbances were significant at nearly every time point of the study, indicating the persistence of these symptoms across active survivorship. Of interest is the significant decrease of fatigue at the end of treatment,

while worry dramatically increased at the end of treatment; worry was only significant during the diagnostic and end of treatment periods although demonstrates an inverse relationship to fatigue at treatment end.

Interventions exist to relieve these common symptoms related to early breast cancer and perhaps need to be explored as to their use, effectiveness, and value. Perhaps women do not readily identify the presence or severity of symptoms, or do not report them to their providers. Additionally, cancer patients often 'expect' to endure certain symptoms as heard or learned by previous experiences with friends, relatives, work, or other personal experiences. Women with breast cancer need to be educated about the common occurrence of symptoms and the need to report them so that early interventions may be provided.

Fatigue is a complex and debilitating symptom and outcome of a cancer diagnosis and related treatment. These analyses indicate that psychological (e.g. depression, worry) and physiological (e.g. fatigue, pain) factors that are individually and collectively significant may create a symptom cluster that negatively affect patient outcomes and should be addressed early in the diagnostic period and on a regular basis throughout treatment. We need to utilize research results such as these in the clinical setting to motivate discussion among providers and devise systematic interventions to prevent or better treat specific symptoms that can individually or collectively improve outcomes. Non-pharmacologic and pharmacologic interventions may significantly affect individual symptoms and ultimately, fatigue.

While these findings are not complete in their analyses, they do provide a cluster of symptoms that are commonly experienced by women with a new diagnosis of breast cancer. Providers have the ability to start an early discussion with patients regarding symptoms they may experience throughout their treatment. The multidisciplinary treatment team can create a

comprehensive, standardized plan of care that identifies and eliminates these symptoms early on before patients experience unnecessary side effects.

Limitations of the Study

Our secondary analyses were successful in identifying the most bothersome symptoms during diagnosis, active treatment, and its end. It allowed us to determine the peak time periods in which women may experience these symptoms and provide opportunities to correlate interventions on an individual basis. The number of participants in this sample (N=150) and the broad inclusion criteria allowed a wide variety of patient characteristics with needs that can be representative of the population. The study site is a freestanding comprehensive breast center with a multidisciplinary team under one roof. The setting provides a wide variety of practice techniques and interventions and therefore, the study population is representative of multiple approaches to symptom management. Providers at the comprehensive breast center include medical, surgical, and radiation oncologists, accompany registered nurses and nurse practitioners to each provider, and a multidisciplinary team that provides care to our women with breast cancer and participants in this study.

The use of a longitudinal study with repeated measures enabled ongoing measures that provided reliability of findings. These study results are valid due to the study design and use of valid measures. The distress thermometer and its 38-item problem list may be an effective tool to communicate needs on a regular basis without significant time consumption in clinic.

Limitations of this study include one institution which decreases generalizability of the findings. Nevertheless, this study provides a framework for measurements of symptoms, interventions, and outcomes. A future multi-institutional study would expand generalizability.

Conclusion

Women that are newly-diagnosed with breast cancer must undergo a series of interventions that may include surgery, chemotherapy, or radiation therapy. The diagnosis itself as well as side effects from interventions may cause unpleasant symptoms that are difficult and can alter one's lifestyle and quality of life. Research with self-reported problems is important to identify bothersome symptoms that are commonly experienced, and measure the potential effect on the cancer experience. All cancer providers should focus on patient complaints of pain, worry, depression, sleep disturbances, and fatigue to identify appropriate interventions that may ameliorate or eliminate unpleasant symptoms.

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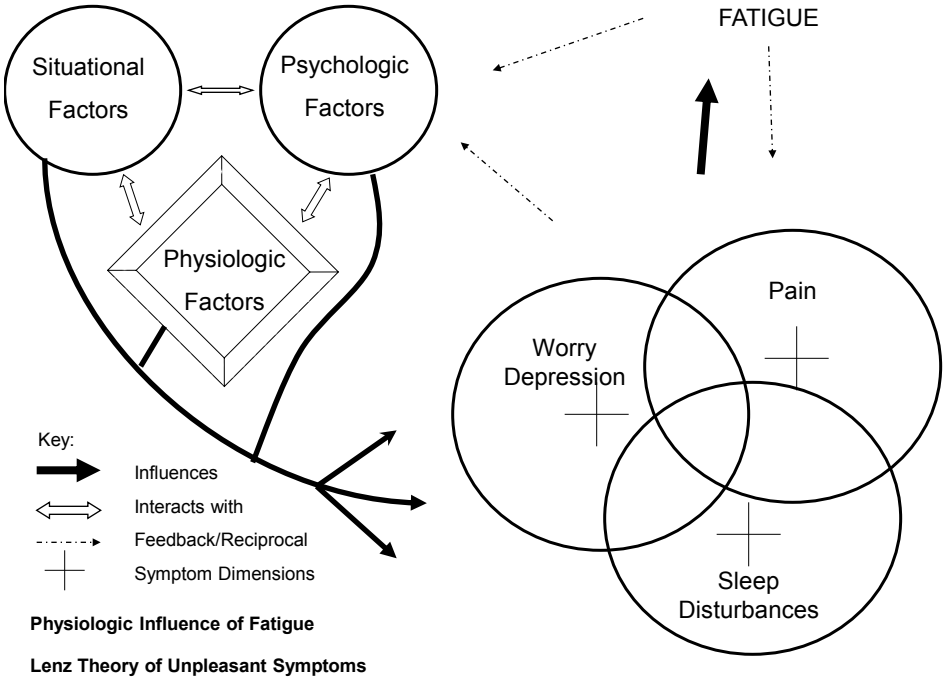
Figure 1. Lenz theory of unpleasant symptoms as related to self-reported symptoms of newly diagnosed women with breast cancer, during active treatment, at its end, and up to 3 months later. The bothersome symptoms as identified in the study included pain, worry, depression, and sleep disturbances, and their effect of performance/fatigue.



Adapted with permission from Lenz, E. and Pugh, L., 2008.

Table 1. The presence or absence of specific symptoms (sleep disturbances, worry, depression, pain, and fatigue) at specific time points during active treatment on the breast cancer trajectory. Significant relationships of time (groups) x symptom are displayed.

Presence of Sleep Disturbances	Time Period	Significance
53%	At diagnosis	*P*=0.7
48%	During treatment	
48%	During treatment	
48%	End of treatment	
Worry	**Time Period**	**Significance**
3%	At diagnosis	*P*=0.004*
17%	During treatment	
17%	During treatment	
24%	End of treatment	
Depression Some of the Time	**Time Period**	**Significance**
32%	At diagnosis	*P*=0.5
30%	During treatment	
35%	During treatment	
38%	End of treatment	

Presence of Pain	Time Period	Significance
38%	At diagnosis	*P*=0.6
28%	During treatment	
35%	During treatment	
31%	End of treatment	

Presence of Fatigue	Time Period	Significance
56%	At diagnosis	*P*=0.001*
58%	During treatment	
49%	During treatment	
34%	End of treatment	

*Indicates significant relationship between fatigue and specific symptom at designated time period.

$P < 0.05$

Table 2. Relationships between fatigue and individual symptoms (worry, depression, pain, and sleep disturbances) at 4 time periods (diagnosis, active treatment, active treatment, end of treatment) and their significance.

Fatigue	Time Period	Significance
Worry	Dx, Tx, **Tx,** End	*P*=0.5, **0.00***, 0.1, **0.01***
Depression	**Dx, Tx, Tx, End**	***P*<0.00*, 0.00*, 0.05*, 0.004***
Pain	**Dx, Tx, Tx, End**	***P*<0.00*, 0.001*, 0.00*, 0.00***
Sleep	**Dx, Tx, Tx, End**	***P*<0.00*, 0.03*, 0.00*, 0.00***

*Indicates significant relationship between fatigue and specific symptom at designated time period.

P< 0.05

Table 3. Results of linear stepwise regression to determine significant effects of individual symptoms on fatigue.

Model	Sum of Squares	df	Mean Squares	F	Significance
1. Regression	14.575	1	14.575	66.009	.000[b]
2. Regression	20.199	2	10.100	48.197	.000[c]
3. Regression	22.635	3	7.545	36.822	.000[d]
4. Regression	23.463	4	5.866	28.808	.000[e]

$P<0.05$

a. Dependent Variable: Fatigue

b. Predictors: (Constant), Sleep

c. Predictors: (Constant), Sleep, Depression

d. Predictors: (Constant), Sleep, Depression, Pain